

1-4. Applicants note with appreciation that the amendments of Paper 17 have been entered in full.

Claims 1-51 are pending claims in the present application. Applicants note that claims 12, 24-29, 32-40, 42, 43, and 49 are withdrawn from consideration, and claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50, and 51 were elected with traverse.

Applicants' correction of the specification obviates the objections.

5-6. Claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 are rejected under 35 U.S.C. 101 for allegedly lacking either a credible asserted utility or a well established utility. Specifically, the Examiner alleges that the term "preventing" requires that no cell or tissue presents any symptoms of the disorder following treatment. Applicants contend that given the limitations of medical science in monitoring every cell in the body, one of skill in the art would not reasonably expect that the term "preventing" was intended to require the absolute lack of symptoms in every cell. Nevertheless, to expedite prosecution, Applicants have amended the claims to more explicitly point out the utility of the claimed methods for treating or improving the functional performance of neurons in an animal. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Furthermore, Applicants contend that since one of skill in the art would not require the term "preventing" to require the absolute absence of symptoms in every cell, Applicants' amendments do not narrow the scope of the claims.

Applicants submit that the amended claims have credible utility for the treatment of neuropathy, and that the foregoing amendments obviate the rejection. Accordingly, reconsideration and withdrawal of this rejection is requested.

7-8. Claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to point out and distinctly claim the subject matter which applicant regards as the invention. To expedite prosecution, Applicants

have amended the claims to incorporate the Examiner's suggestions. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

- a. Applicants' amendment of the terms '*hedgehog* therapeutic' and '*patched* therapeutic' obviates the rejection.
- b. Applicants contend that the term *hedgehog* polypeptide was well known in the art, at the time of filing, and is described in detail in the specification such that one of skill would readily recognize the metes and bounds of the claimed subject matter. Nevertheless, to expedite prosecution, Applicants have amended the claims to define the claimed *hedgehog* polypeptides with respect to the disclosed sequences. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.
- c. Applicants contend that the term "therapeutically effective" is defined in the specification (pages 11 and 59) such that one of skill in the art can recognize the metes and bounds of the claimed subject matter. Nevertheless, to expedite prosecution, Applicants have amended the claims. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.
- d. Applicants' amendment of the term 'homology' obviates the rejection.
- e. Applicants contend that the term 'stringent conditions' is art recognized. The claims recite the term "stringent" to characterize the hybridization conditions. In the parlance of the molecular biologist the composite term "stringent (hybridization) conditions" has come to signify those conditions of heat and salt which are standard for the detection of genes in mammals using a hybridization-dependent detection method such as a Southern Hybridization (see e.g. pg. 9.47-9.57 of Sambrook, Fritsch and Maniatis (1989) Molecular Cloning, 2nd ed., Cold Spring Harbor Press). Thus, to one of skill in the art, the expression "stringent" is not ambiguous. Nevertheless, to expedite prosecution, Applicants have amended claim 10 to explicitly specify the stringency conditions. This amendment is not made in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.
- f. Applicants have amended claim 41 to provide proper antecedent basis.

9-10. Claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the claims allegedly fail to enable for methods of treating all neuropathies, and methods for treating neuropathy with a therapeutic other than a *hedgehog* polypeptide. Applicants traverse this rejection to the extent that it is maintained over the amended claims.

The Examiner points out that Applicants have enabled “for methods of treating and protecting against cisplatin and taxol induced neuropathy and a neuropathy resulting from sciatic nerve crush, or viral induced neuropathy or hereditary amyotrophic lateral sclerosis.” However, the Examiner further maintains that Applicants have failed to provide enablement for the treatment of other neuropathies including diabetic neuropathy.

Applicants point out that in accordance with MPEP 2164.02, “[a]n example may be either working or prophetic. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.” As pointed out by the Examiner, Applicants have provided several working examples demonstrating the efficacy of *hedgehog* agonists in treating neuropathy. Applicants have also disclosed prophetic examples. These prophetic examples can be easily evaluated based on the methods disclosed by Applicants. Given the present application, the efficacy of *hedgehog* agonists in treating any of the wide range of neuropathies can be readily evaluated without undue experimentation. This is the standard under MPEP 2164.08(b) which states that “[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.”

Applicants have demonstrated the efficacy of the invention in treating peripheral neuropathies successfully in several distinct *in vivo* models. This demonstrates that the claimed methods are broadly enabled for the treatment of a diverse array of neuropathic conditions.

Applicants cannot be expected to wait for laboratory animals to spontaneously develop neuropathy in order to test the claimed methods in every potential cause of peripheral neuropathy. This sentiment was echoed by the Federal Circuit in *In re Brana*. In addressing whether the invention satisfied the utility requirement, the Court found that the applicants' experimental evidence in a particular tumor model was sufficient evidence of the utility of the invention. Furthermore, the Court pointed out that if scientists were required to wait until animal models for all diseases were developed or occurred spontaneously, there would be no effective way to conduct medical experiments. (*In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 Fed Cir. 1995). Applicants thus submit that absent evidence that the various types of neuropathy are not amenable to reasonably consistent treatment methods, that the methods employed by Applicants' are representative of peripheral neuropathy generally.

The Examiner has cited only one reference to suggest that one of skill would have reasonable basis to presume that *hedgehog* agonists would not function as disclosed by Applicants (Oppenheim et al., 1999). Applicants remind the Examiner that the determination of enablement must be made based on an evaluation of the evidence as a whole (MPEP 2164.05). The consideration of this reference over the preponderance of the evidence presented by both Applicants and by others in the art constitutes unfair picking and choosing of references. Furthermore, the significant differences between the model system employed by Applicants and that employed by Oppenheim et al. make this particular reference irrelevant to the claimed subject matter. This argument is made most eloquently by Oppenheim et al. "In view of the report that Shh can promote the survival of cultured rat embryo spinal interneurons (Miao et al., 1997), the present negative results with chick embryo interneurons were, on the face of it, unexpected. However, unlike rat and mouse embryos, spinal interneurons in the chick represent one of the few neuronal populations in which PCD of postmitotic cells does not occur naturally. Therefore, it is perhaps not surprising that interneuron numbers were unaffected by Shh." (Oppenheim et al., 1999, page 353 column 2-page 355 column 1). Although Oppenheim et al. presents seemingly contradictory evidence, the differences between the anatomy of their system and mammalian neural anatomy make any comparisons between their work and Applicants work tenuous, especially when corroborative evidence using mammalian systems exists. Furthermore, there is no evidence presented to suggest that peripheral neurons undergo PCD or are otherwise similar to the chick spinal interneurons of Oppenheim et al. Finally, as reviewed in detail in the

specification (pages 1-3), peripheral neuropathies are conditions of the peripheral nerves and affect motor, sensory, and autonomic nerves. The spinal interneurons studied by Oppenheim et al. are not the ultimate mediators of peripheral neuropathy, and are distinct phenotypically from the neurons that degenerate in peripheral neuropathy. Thus, whether they are affected by *hedgehog* signaling in this chick model is not relevant to the enablement of the claimed subject matter.

The claims are additionally rejected for allegedly failing to enable for treatment with agonists other than a *hedgehog* polypeptide. Applicants maintain that the *hedgehog* signaling pathway is presented in detail in the specification (page 52, line 31-page 53, line 15), and furthermore that this pathway is well known in the art. Applicants have additionally provided a detailed description of small molecule *hedgehog* agonists including inhibitors of PKA (page 55, line 6-page 57, line 5). Furthermore, Applicants provide high throughput screens that could be used to identify other small molecule *hedgehog* agonists. Applicants have provided a detailed definition of *hedgehog* agonists, and the functional characteristics that exemplary *hedgehog* agonists would possess. These functional characteristics would allow one to identify small molecule agonists without undue experimentation.

The Examiner has cited Stull and Iacovitti to argue that the details of *hedgehog* signaling are still unpredictable. Applicants contend that this reference is not applicable to the present invention. Stull and Iacovitti analyze the ability of Shh to augment or alter the effects of various FGFs on neural cultures. None of the experiments of Stull and Iacovitti examine the effects of Shh administered in the absence of FGFs. Therefore, it is impossible to evaluate the effects of agonizing *hedgehog* signaling in this system because *hedgehog* signaling is never examined. All that can reasonably be inferred from these experiments is that some ill-defined interaction between hyperactivation of FGF signaling and *hedgehog* protein may inhibit *hedgehog* signaling. Applicants' invention requires agonizing *hedgehog* signaling. Since this experiment was never addressed by Stull and Iacovitti, it is not sound to apply their conclusions to Applicants' data.

Applicants contend that the amended claims are enabled throughout their scope. Applicants present working examples demonstrating the use of *hedgehog* agonists in the treatment of several distinct types of peripheral neuropathy. The specification also enumerates in

great detail other neuropathies that could be treated by the methods of the invention, as well as other agonists that could be used in the treatment of neuropathy. The efficacy of these prophetic embodiments of the invention can be readily evaluated by one of skill in the art without undue experimentation. Applicants have provided extensive discussion of methods which can be used to evaluate these prophetic embodiments, and the understanding of *hedgehog* signaling in the art is very high. Furthermore, Applicants contend that the references cited by the Examiner asserting the unpredictability of the art with respect to *hedgehog* signaling are not applicable to the claimed invention and should not be considered in the face of the extensive evidence presented by Applicants. Accordingly, reconsideration and withdrawal of this rejection is requested.

11. Claims 1-8, 10, 11, 13, 14, 16-23, 30, 31, 41, 44, 45-47, 48, 50, and 51, are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse this rejection to the extent that it is maintained over the amended claims.

Applicants have amended the claims to more explicitly point out that the claimed therapeutics are *hedgehog* agonists. *Hedgehog* agonists are defined as “a *hedgehog* therapeutic which mimics or potentiates the activity of a wild type *hedgehog* protein.” (page 10, lines 24-26). Such *hedgehog* agonists are described in detail in the specification which provides both examples and functional characteristics of *hedgehog* agonists.

The *hedgehog* pathway is described in detail (page 52, line 31-page 53, line 15), as are the identified *hedgehog* polypeptides (page 19, line 14-page 21, line 7). In addition to this detailed general description of the *hedgehog* pathway and *hedgehog* polypeptides, Applicant specifically described the *hedgehog* polypeptides of the invention (page 4, lines 3-9). “[T]he hedgehog protein has an amino acid sequence at least 60, 75, 85, or 95 percent identical with a *hedgehog* protein of any of SEQ ID Nos. 10-18 or 20, though sequences identical to those sequence listing entries are also contemplated. The *hedgehog* protein can be encoded by a

nucleic acid which hybridizes under stringent conditions to a nucleic acid sequence of any of SEQ ID Nos. 1-9 or 19."

One of skill in the art would have been able to recognize which compounds are *hedgehog* agonists because Applicants defined a *hedgehog* agonist as one "which mimics or potentiates the activity of a wild type *hedgehog* protein". Additionally, Applicants provide examples of the functional properties of *hedgehog* agonists which include "compounds which bind to *patched* and alter its signal transduction activity, compounds which alter the binding and/or enzymatic activity of a protein involved in *patched* signaling pathway, and compounds which alter the level of expression of a *hedgehog* protein, a *patched* protein, or a protein involved in intracellular signal transduction pathway of *patched*."

The *hedgehog* agonists of the invention also include small organic molecules. Applicants have provided a detailed description of one class of exemplary small molecule *hedgehog* agonists: PKA inhibitors (page 55, line 6-page 57, line 5). Additionally, Applicants provide a detailed discussion of high-throughput screens which could easily identify additional small molecule agonists (page 48, lines 6-26). Such high-throughput screens were well known in the art at the time of filing, and one of skill could easily identify, without undue experimentation, small molecule *hedgehog* agonists which would fulfill the criteria enumerated in the disclosure.

The term *hedgehog* agonist is described in detail throughout the specification such that one of skill in the art could easily envision the polypeptides and small molecules of the invention. Such compounds must fulfill the functional criteria of activating/stimulating *hedgehog* signaling, and Applicants have even provided several experimental measures that would allow one of skill to readily recognize the claimed subject matter. Accordingly, reconsideration and withdrawal of this rejection is requested.

12-13. Claims 1-4, 6-11, 13-18, 21, 30, 31, 41, 44-48, 50, and 51 are rejected under 35 U.S.C. 102(b) for allegedly being anticipated by WO95/18856, Ingham et al. Applicants respectfully traverse this rejection to the extent that it is maintained over the amended claims.

Ingham et al. fails to satisfy the criteria for anticipating Applicants' invention. Both the MPEP and the Federal Circuit support Applicants' contention that in order to anticipate or render obvious the claimed invention, the cited art must teach all the limitations of the claimed subject matter. (MPEP 2131). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."

Verdegall Bros. v. Union Oil Company of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ3d 1913, 1920 (Fed. Cir. 1989). The Ingham et al. application fails to teach the particular combination of elements of the pending claims.

Nor is the claimed subject matter obvious in view of the teachings of Ingham et al. Applicants contend that a valid patent may issue for a nonobvious species related to a prior patented invention, even though the improvement falls within the claims of that prior patent. A prior genus which does not explicitly disclose a species does not anticipate a later claim to that species. This position is well supported by the holdings of the Federal Circuit. See, for example, *Corning Glass Works v. Sumitomo Electric U.S.A.*, 868 F.2d 1251, 1262, 9 USPQ2d 1962, 1970 (Fed. Cir. 1989) ("a patent claiming germania as a dopant for the fused silica core of an optical waveguide fiber, the germania providing the advantages of not requiring a heat treatment and of transmitting more light than the titania dopant previously used, was not anticipated by a publication that described waveguide fibers with doped cores; the publication did not expressly disclose germania but did not exclude it; the accused infringer's anticipation argument 'approximates one for infringement, rather than inherency, and is confusing at best....Under [its] theory, a claim to a genus would inherently disclose all species....]The publication] is a reference only for that which it teaches.'").

Applicants contend that the relationship between the pending claims and the cited art is largely analogous to the factual situation in the above example. Applicants assert that the presently claimed invention is a species which is unobvious and patentable over the generic teachings of Ingham et al.

Prior to the Applicants' disclosure, one of skill in the art could not have reasonably anticipated that systemically administered polypeptides would persist in the body for a period of time and in a sufficient dosage to provide the level of efficacy for treating peripheral neuropathy, as was observed in the present case. For instance, one of skill could not have been able to predict the degree to which systemically administered hedgehog polypeptides would correctly localize to peripheral nerves in sufficient concentration to be therapeutically effective. Applicants present abundant evidence demonstrating the efficacy of systemically applied *hedgehog* polypeptides in treating neuropathy. Applicants' Example 1, for example, details the results of systemically administering *sonic hedgehog* to mice treated with cisplatin. That such systemic treatment would work as well as demonstrated to treat neuropathy could not have been anticipated prior to the teachings of the present application which demonstrated the unexpected benefits of such a combination.

Applicants contend that Ingham et al. fail to meet the limitations set forth in the claims. Although Ingham et al. broadly teaches compositions and methods using *hedgehog* polypeptides, Ingham et al. fail to teach the benefits of the particular combinations of agents and mode of administration set forth in the pending claims. That is, although Ingham et al. broadly teaches methods using *hedgehog* polypeptides, Ingham et al. provides no motivation to specifically select systemic administration to treat peripheral neuropathy, the embodiment to which the pending claims are directed. MPEP 2144.08 outlines the guidelines for determining that a reference renders an invention obvious and directs the Examiner to "determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus." Applicants contend that Ingham et al. fails to provide motivation to select methods of using systemic administration to treat peripheral neuropathy. Furthermore, the Examiner has not provided any evidence or additional references that would have motivated one of skill in the art to arrive at Applicants' invention.

Given that the cited art fails to meet all the limitations set forth in the claims, and that the cited art provides no motivation to specifically select systemic administration to treat peripheral neuropathy as the species to which the claims are directed, the cited art fails to meet the

standards for anticipating or rendering obvious the claimed invention. Reconsideration and withdrawal of this rejection is requested.

14-15. Claims 1-4, 6-11, 13-18, 21, 30, 31, 41, 44-48, 50, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO95/18856, Ingham et al., in light of Porter et al. Furthermore, the claims are rejected under 35 U.S.C. 103(a) as being unpatentable over WO95/18856, Ingham et al., in light of Pepinsky et al. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have discussed in detail above why Ingham et al. does not anticipate Applicants invention. Both Pepinsky et al. and Porter et al. teach lipophilic modifications of *hedgehog* polypeptides. However, neither reference overcomes the deficiencies of Ingham et al. with regard to systemic administration of *hedgehog* polypeptides. Therefore these references, even when combined, do not overcome the deficiencies of Ingham et al. Accordingly, reconsideration and withdrawal of the rejection is requested.

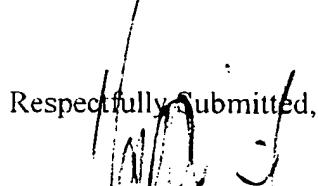
16. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO95/18856, Ingham et al., in light of Jonassen et al. Applicants traverse this rejection to the extent that it is maintained over the amended claims.

As outlined above, Applicants' invention is not anticipated by Ingham et al. because Ingham et al. does not demonstrate that *hedgehog* polypeptides can be used to systemically treat neuropathy. Jonassen et al. teaches specific modifications of *hedgehog*. However, this reference does not overcome the deficiencies of Ingham et al. to lead one of skill in the art to expect that the polypeptide would have efficacy upon systemic administration. Accordingly, reconsideration and withdrawal of this rejection is requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1948**.

Respectfully Submitted,


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